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(71) Applicant(s)
LTS Lohmann Therapie-Systeme GmbH

(72) Inventor(s)
Bodo Asmussen; Karsten Cremer; Walter Muller

(74) Agent/Attorney
DAVIES COLLISON CAVE,GPO Box 3876,SYDNEY NSW 2001

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(71) Anmelder (*für alle Bestimmungsstaaten ausser US*): LTS LOHMANN THERAPIE-SYSTEME GMBH ~~& CO. KG~~ [DE/DE]; Irlicher Strasse 55, D-56567 Neuwied (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder (*nur für US*): ASMUSSEN, Bodo [DE/DE]; Im Schloßgarten 10, D-56170 Bendorf-Sayn (DE). CREMER, Karsten [DE/DE]; Eifelstrasse 4a, D-53119 Bonn (DE). MÜLLER, Walter [DE/DE]; Engerser Strasse 56, D-56565 Neuwied (DE).

(74) Anwalt: FLACCUS, Rolf-Dieter; Sperlingsweg 32, D-50389 Wesseling (DE).

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(54) Title: ACTIVE SUBSTANCE CARRIER FOR THE CONTROLLED RELEASE OF ACTIVE SUBSTANCES IN THE GASTRO-INTESTINAL TRACT WITH DELAYED PASSAGE THROUGH THE PYLORUS

(54) Bezeichnung: WIRKSTOFFTRÄGER ZUR KONTROLLIERTEN FREISETZUNG VON WIRKSTOFFEN IM GASTROINTESTINALTRAKT MIT VERZÖGERTER PYLORUSPASSAGE

(57) Abstract

A strip-shaped film substrate with openings and loaded with an active substance serves as the basis for the production of an active substance carrier for the controlled release of active substances in the gastro-intestinal tract with delayed passage through the pylorus.

(57) Zusammenfassung

Ein bahnförmiges, folienartiges, mit Öffnungen ausgebildetes und mit Wirkstoff beladenes Substrat wird als Ausgangsmaterial verwendet zur Herstellung eines Wirkstoffträgers zur kontrollierten Freisetzung von Wirkstoffen im Gastrointestinaltrakt mit verzögerter Pyloruspassage.

ABSTRACT

A web-shaped, sheet-like substrate provided with openings and charged with active substance is used as starting material for the manufacture of an active substance carrier for the controlled release of active substances in the gastrointestinal tract which has a delayed pylorus passage.

Active substance carrier for the controlled release of active substances in the gastrointestinal tract with a delayed pylorus passage

The present invention relates to the use of a web-shaped, sheet-like substrate provided with openings and loaded with active substance.

Active substance carriers and administration forms having a prolonged retention time in the stomach are used to make possible a local therapy of stomach diseases. In addition, they permit the release of active substances over a period which altogether is longer than that of conventional peroral administration forms so that the frequency of intake can be reduced.

A prolonged residence time in the stomach is provided by administration forms which either have a particularly low density and float on the gastric juice or cannot pass the pylorus owing to their size or bulkiness.

For example, floating administration forms are those having a large portion of lipophilic, low-density substances (DE 26 11 041). In addition, there are descriptions how a delayed-action tablet or capsule can be caused to float by means of a plurality of air inclusions (EP-A 0 297 978, DE-A 38 03 482). Finally, gas-producing substances or mixtures, for example, CO_2-producing effervescent mixtures, can be incorporated into an enclosed administration form; this at the same time results in an expansion of such a device after application (US 4 996 058).

A great disadvantage of the floating administration forms is their unreliable gastro-retentivity. As long as their passage through the

pylorus is not additionally impeded by their size (EP-A 0 308 904), flotation takes place only in persons sitting or standing upright. In case of lying persons the pylorus is likely to come into contact with the surface of the gastric juice, with the floating administration form being preferentially transported into the small intestine (A.J. Moës, Crit. Rev. Therap. Drug Carrier Syst. 10, 143, 1993). Additionally, flotation of such devices requires the presence of a minimum amount of gastric juice, this, however, cannot always be supposed in patients.

Administration forms retained in the stomach because of their size or bulkiness have also been known for a long time now. Since the administration form is to be swallowed and must therefore not exceed a certain maximum dimension, different mechanisms used to enlarge the device in the stomach after application have been described. For example, this can be achieved by providing a gas phase in the device after contact with aqueous liquid (US 4 996 058), or by swelling of hydrophilic components in the gastric juice (EP 0 425 154, US 5 147 646, EP 0 310 326, US 4 207 890, US 4 434 153). The disadvantage of these administration forms primarily lies in the fact that they either have an insufficient stability to resist the contractile forces produced by the musculature of the stomach wall or - in case they have this strength - involve the risk of resulting in an undesired and probably dangerous pylorus obstruction which prevents the further transport of the remaining gastric contents.

Also, differently shaped, bulky active substance-carrying devices are known which, for application purposes, are present in a compressed or contracted form first. In this connection, the compressed or contracted state is generally fixed by means of enclosures, such as capsules, until these disintegrate in the gastric juice. After disintegration of the enclosure, recovery forces or the swelling pressure of hydrophilic components cause the bulky

structures to revert to their original shape (US 4 735 804, EP 0 202 159, US 5 002 772, EPA 0 415 671).
As long as their mechanical stability is sufficient to resist the gastric contraction, they might be best suitable as gastro-retentive administration forms because the pylorus passage is prevented reliably and emptying the remaining stomach contents is not impeded.

In contrast to construction features of various gastro-retentive systems, aspects with respect to production engineering are only scarcely described in the art. Owing to the complex shaping of the known gastro-retentive administration forms, the industrial series production of such systems involves considerable effort and capital cost. Continuous processes have not been described as yet. Gastro-retentive administration forms frequently comprise different components serving either the conservation of the shape or the active substance release. Also, there are no pharmaceutical test methods ensuring the quality of these administration forms during production. Large and unwieldy structures having a high mechanical stability are difficult to manufacture; in addition, it is disadvantageous that they may cause stomach irritations.

It is a preferred object of the present invention to provide an active substance carrier for the controlled release of active substances in the gastrointestinal tract with a delayed pylorus passage, which avoids or even overcomes the above-mentioned disadvantages and difficulties, permits a considerably prolonged retention time in the stomach under release of active substances during a local therapy of the stomach or the gastric mucous membrane, facilitates the oral application to a very high degree, and is suitable for an economically efficient series production.

Thus the present invention proposes the use of an active substance carrier in web form provided with openings and a

substrate charged with active substance as starting material for the production of an active substance carrier for the controlled release of active substances in the gastrointestinal tract and which exhibits a delayed pylorus passage.

In particular, the present invention provides a pharmaceutical composition for oral administration of an active substance to be released in a controlled manner within the gastrointestinal tract, the pharmaceutical composition comprising at least one said active substance contained within a sheet-like active substance carrier provided with openings of ≥3 mm in diameter and which expands, unfolds or spreads upon contact with gastric juice to give an area of ≥5 cm^2.

The present invention also provides a process for the production of a pharmaceutical composition as immediately preceding comprising the steps of loading with at least one active substance a web-shaped sheet-like material provided with openings of ≥3 mm in diameter and forming the material of discrete area sizes of ≥ 5 cm^2 into a compacted form as a rolled or folded compressed article.

The material of the active substance carrier is very advantageous in many respects. It permits an economic production by using known, continuous processes for processing web-shaped, sheet-like material, such as winding up and off, coating and punching, as well as encasing with a material promoting the coherence. The gastro-retentive embodiments which can be produced thereby have additional advantageous properties. For instance, owing to the sheet-like design of the active substance carrier, irritations of the gastric mucosa are not - or only to a very slight degree - to be expected; these occur when the known three-dimensional bulky structures are used which are retained in the stomach because of their size and bulkiness. In particular when the device which unfolds in the gastric juice after erosion of the casing has a sufficient mechanical

stability, a high reliability with respect to the gastro-retentivity is to be expected. At an obtainable minimum expansion of 5 cm^2, the active substance carrier is greater than the opening of the human pylorus, with the maximum expansion to up to 8 cm^2 providing an even greater certainty of preventing the pylorus passage. As compared with most of the previous systems, wherein the passage through the pylorus takes place as soon as the stomach musculature succeeds in reducing the device to a sufficient extent, better adjustment of the intended residence time of the active substance carrier in the stomach is achieved. Since the degree of stomach contractions depends on a great variety of factors which can hardly be controlled in practice, for example, the activity state of the autonomic nervous system, in particular that of the parasympathetic nervous system, the retention time of the administration forms proposed so far may well be subject to a high degree of individual variability when in use. In contrast to

this, the retention time of the active substance carrier according to the present invention can be adjusted with a considerably higher reliability by means of the galenic formulation: the composition determines the rate at which the device in the gastric juice - mainly by means of erosion - loses the properties causing its retention.
The fact that the active substance carrier is provided with apertures counteracts the danger of an unintentional pylorus obstruction. As a rule, the pylorus allows the passage of liquid material having a low to medium viscosity and of particulate material having a particle size of up to about 2 mm. If, for example, the active substance carrier has openings of 3 mm or more in diameter, it is ensured that an undesired pylorus obstruction cannot take place. Even in case the device should lie down over the pylorus opening, it would merely cause a screening effect.

According to one embodiment of the present invention, the active substance carrier comprises at least one active substance developing a local effect in the stomach. This may be an active substance which is preferably absorbed by the gastric mucosa. However, it may also be an active substance for which an absorption window exists in the upper portion of the small intestine. Thus, the subject matter of the present invention is also suitable for the administration of active substances developing their effect in the upper portion of the small intestine. So far, conventional peroral depot forms have not been suitable for this purpose, since they release most of the dose not until having left the upper region of the small intestine. The active substance carrier according to the present invention can ensure that released active substance in dissolved form is supplied to the upper small intestine in an even manner over a prolonged period of time.

The present invention has several therapeutic advantages. On the one hand, it permits a considerably improved local treatment of

stomach diseases, as compared with conventional administration forms. These particularly include the hyperacidity, microbial infections, the gastritis, and the ulcer. Efficacious drugs are available for the treatment of these and other stomach diseases; their effectiveness and therapeutic index, respectively, is increased by the fact that they are administered by means of the active substance carrier according to the present invention. Thereby a particularly large portion of the applied active substance dose is brought into immediate contact with the affected tissue. The period of local exposure to effective drug concentrations is increased. Examples of such active substances include mineral antacids, H_2-receptor blockers, such as cimetidine, ranitidine, famotidine, nizatidine, roxatidine, and their salts; muscarine receptor blockers, such as pirenzipine; so-called proton pumps, such as omeprazol and misoprostol; drugs which are effective against heliobacter pylorii and other microbial noxae, such as proglumide and carbenoxolone.

According to an embodiment, the active substance carrier additionally comprises gaseous substances, gas-producing substances and mixtures, or liquid and solid substances and/or their mixtures, having a relative density of < 1. This supports the retention of the active substance carrier in the stomach by the fact that - in addition to the size of its area - it becomes a floating device.

According to the present invention, the active substance carrier consists of or comprises a material which is erodible in biological liquids, and in effect is erodible in the fluid milieu of the gastrointestinal tract. The composition of the material that is used substantially determines the retention time of the gastro-retentive device in the stomach. It is preferred that it consist of one or several physiologically acceptable polymers and further pharmaceutical adjuvants, for example, softening agents, wetting agents, hydrophilizing agents, stabilizers, dyes, release agents, buffer salts, and the like. Examples of the polymers to be used include polysaccharides, such as gums, starch or cellulose derivatives; polyacrylates and

polymethacrylates; polylactides, polyglycolides, poly(oxyethylenes) and polyoxypropylenes; proteins, poly(vinyl alcohol), poly(vinyl acetate), poly(vinyl chloride), or poly(vinyl pyrrolidone); silicone elastomers, and copolymers. By using suitable mixtures an erosion rate can be adjusted which achieves the intended retention time in the stomach. At the end of this period, a device manufactured according to the present invention has lost its mechanical stability to a degree that allows its size reduction by the gastric contraction and thus its passage through the pylorus. At the end of this period, an active substance carrier produced according to the present invention has lost its mechanical stability to a degree that allows its size reduction by gastric contractions and thus its passage through the pylorus.

The dimensions of active substance carriers that can be manufactured according to the present invention are changed by means of rolling or folding them in such a manner that they are rendered suitable for a peroral application. This implies that the sheet-like material be flexible and not brittle. After rolling up or folding, the devices are preferably provided with a suitable enclosure which keeps them in this state until application. A hard gelatin capsule, for example, is such a casing; however, any other envelope is suitable which holds the device in its rolled or folded state, disintegrates in the gastric juice, and is pysiologically acceptable.

As a whole the active substance carrier is superior to the state of the art by a great variety of advantages. These include the fact that the active substance carrier makes it possible in a long-term therapy to reduce the frequency of taking to an extent by far exceeding that of conventional sustained-release forms. In general, depot drugs are useful in the long-term therapy if the active substance is eliminated from the body very quickly, i.e., at an elimination half-life of less than about 10-20 h. In case the intake frequency can be reduced by means of sustained-release forms,

extreme variations of the blood level and with the undesired side effects can be avoided and the patient compliance be improved. When the active substance carrier according to the present invention is used, the intake frequency of many active substances can be reduced to a once-a-day dose which represents another progress in the therapeutic safety.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The claims defining the invention are as follows:

1. A pharmaceutical composition for oral administration of an active substance to be released in a controlled manner within the gastrointestinal tract, the pharmaceutical composition comprising at least one said active substance contained within a sheet-like active substance carrier provided with openings of ≥3 mm in diameter and which expands, unfolds or spreads upon contact with gastric juice to give an area of ≥5 cm^2.

2. A pharmaceutical composition of claim 1, wherein the composition in its unexpanded form is surrounded by a casing which disintegrates in the gastric juice.

3. A pharmaceutical composition of claim 2, wherein the casing is a capsule.

4. A pharmaceutical composition of any one of claims 1 to 3, wherein at least one active substance can develop a local action in the stomach.

5. A pharmaceutical composition of any one of claims 1 to 3, wherein at least one active substance is absorbed by the gastric mucosa.

6. A pharmaceutical composition of any one of claims 1 to 3, wherein at least one active substance has an absorption window in the region of the upper small intestine.

7. A pharmaceutical composition of any preceding claim, wherein the composition additionally comprises gaseous substances, gas-producing substances or substance mixtures, or liquid and solid substances and/or their mixtures, which have a relative density of <1.

8. A pharmaceutical composition of any preceding claim, wherein the composition consists of or comprises a material which is erodible in the fluid milieu of the gastrointestinal tract.

9. A pharmaceutical composition of any preceding claim, wherein the composition is formed in an orally applicable compacted form as a roll or folded compressed article.

10. A process for the production of a pharmaceutical composition of any one of claims 1 to 9 comprising the steps of loading with at least one active substance a web-shaped sheet-like material provided with openings of ≥3 mm in diameter and forming the material of discrete area sizes of ≥5 cm^2 into a compacted form as a rolled or folded compressed article.

11. A process of claim 10, wherein the pharmaceutical composition is encapsulated.

12. A process of claim 10 or 11, wherein the process is a continuous process.

DATED this 11th day of January 1999

LTS LOHMANN THERAPIE SYSTEME GMBH

By its Patent Attorneys
DAVIES COLLISON CAVE